Registry No.—II, 22423-79-6; III, 22423-80-9; IV, 22423-81-0; V, 5034-33-3; VI, 22423-83-2; VII, 22423-84-3; VIII, 22423-85-4; IX, 19641-75-9.

Acknowledgments.—The authors express their appreciation to the following members of these laboratories: Miss Patricia Evans for the preparation of starting materials, Mrs. Helga Albrecht for infrared spectra, and Mr. David Schlesinger for amino acid analyses.

Sulfur-Containing Polypeptides. X. A Study of β Elimination of Mercaptides from Cysteine Peptides[1-3]

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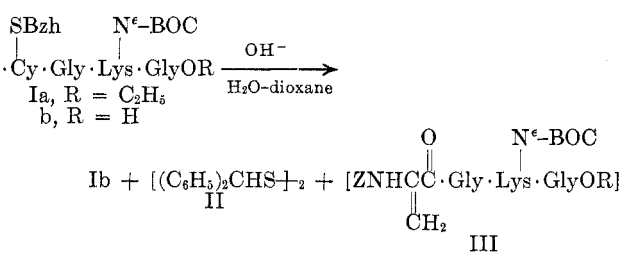
During the attempted saponification of ethyl N-carbobenzoxy-S-benzhydryl-L-cysteinylglycyl-N$^{\epsilon}$-*t*-butyloxycarbonyl-L-lysylglycinate (Ia) using 1 equiv of sodium hydroxide in aqueous dioxane, a mixture of products was obtained. In addition to some of the desired acid, Ib, the presence of several substances of higher mobility was indicated by tlc of the reaction mixture. Subsequently, one of these components was isolated and identified by melting point and mass spectral fragmentation pattern as dibenzhydryl disulfide (II). Presumably, benzhydryl mercaptide and the corresponding dehydroalanine peptide, III, were initially produced by a β-elimination[5-7] reaction; air oxidation of the mercaptide would yield II.



In order to obtain a quantitative evaluation of the extent of β elimination, a procedure devised by Patchornik and Sokolovsky[8] and Gawron and Odstrchel[9] was utilized. These workers have described an analytical method for the acid-catalyzed conversion of peptide-bound dehydroalanine to pyruvic acid and the subsequent determination of the pyruvic acid present using lactic dehydrogenase and reduced diphosphopyridine nucleotide. The amount of pyruvic acid present is assumed to represent the extent of β elimination in the original alkaline reaction. Several S-alkyl-L-cysteine esters were studied using this procedure; the substrates (Table I) included Ia, ethyl N-carbobenzoxy-S-benzyl-L-cysteinylglycinate (IV), ethyl N-carbobenzoxy-S-benzhydryl-L-cysteinylglycinate (V), and ethyl N-carbobenzoxy-S-trityl-L-cysteinylglycinate (VI). In these experiments the substrate was allowed to stand with 1.1 equiv of 1.0 *N* sodium hydroxide for 5 hr, the solvent was evaporated, and the residue was treated with 6 *N* hydrochloric acid solution at 110° for 5 hr. The amount of pyruvic acid was then determined spectrophotometrically. It is apparent from these results that the amount of β elimination is small using hydroxide ion despite the intensity of the dibenzhydryl disulfide spot on the thin layer chromatograms. The amount of pyruvic acid present was not significantly affected by solvent or the nature of the S-alkyl substituent.

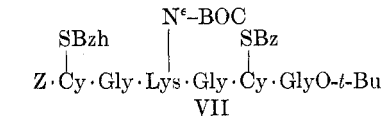
TABLE I

β ELIMINATION OF MERCAPTIDES FROM S-ALKYLCYSTEINE ESTERS DURING ESTER HYDROLYSIS

Peptide	Solvent[a]	Concn of peptide, *M*	β elimination,[b] %
Ia	EtOH	0.01	4.4, 5.0, 5.1, 5.4
Ia	DMF	0.01	4.8
IV	EtOH	0.04	4.8, 5.0, 5.3
V	EtOH	0.04	2.0, 2.3
V	DMF	0.04	2.4, 2.7
VI	EtOH	0.04	1.8
VI	DMF	0.03	1.9

[a] Solutions contain 1.1 equiv of 1.0 *N* sodium hydroxide. [b] Percentage of β elimination is equated to the percentage of pyruvic acid found in the reaction mixture after 5 hr at 25°. Pyruvic acid was determined by the procedure of A. Patchornik and M. Sokolovsky (ref 9).

The amount of β elimination accompanying the removal of an S-benzoyl group from peptides containing both S-benzhydryl- and S-benzoyl-protected L-cysteine residues was then investigated. As expected, methanolysis of *t*-butyl N-carbobenzoxy-S-benzhydryl-L-cysteinylglycyl-N$^{\epsilon}$-*t*-butyloxycarbonyl-L-lysylglycyl-S-benzoyl-L-cysteinylglycinate (VII), using dilute sodium methoxide in methanol solution (0.077 *M*), produced low levels of pyruvic acid (Table II). The hexapeptide, VII, was readily soluble in methanol, and methanolysis of the S-benzoyl group on a preparative scale proceeded rapidly and cleanly, as described by Zervas, *et al.*[10] It was noted, however, that, when the methoxide concentration was increased from 0.001 to 0.02 *M*, a spot corresponding to II appeared on the tlc of the reaction mixture. In contrast to VII, the hexapeptide, *t*-butyl N-carbobenzoxy-S-benzhydryl-



(1) Part IX of this series: R. G. Hiskey and J. T. Sparrow, *J. Org. Chem.*, **35**, 215 (1970).

(2) Supported in part by Grant A-3416 from the National Institute of Arthritis and Metabolic Diseases of the National Institutes of Health, U. S. Public Health Service.

(3) The following abbreviations have been incorporated in the text; Z = carbobenzoxy; BOC = *t*-butyloxycarbonyl; Bzh = benzhydryl; Tr = trityl; Bz = benzoyl; *t*-Bu = *t*-butyl; Cy = cysteinyl; Gly = glycyl; Lys = lysyl.

(4) Abstracted in part from a dissertation by R. A. Upham submitted to the University of North Carolina in partial fulfillment of the requirements for the Ph.D. degree, Aug 1968.

(5) (a) J. A. MacLaren, W. E. Savige, and J. M. Swan, *Aust. J. Chem.*, **11**, 345 (1958); (b) J. A. Maclaren, *ibid.*, **11**, 360 (1958).

(6) L. Zervas, I. Photaki, A. Cosmatos, and N. Ghelis, *Peptides, Proc. Eur. Symp., 6th, 1968*, 27 (1963).

(7) I. Photaki, *J. Amer. Chem. Soc.*, **85**, 1123 (1963).

(8) A. Patchornik and M. Sokolovsky, *ibid.*, **86**, 1206 (1964).

(9) O. Gawron and G. Odstrchel, *ibid.*, **89**, 3263 (1967).

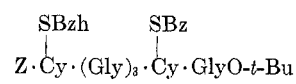
(10) L. Zervas, I. Photaki, and N. Ghelis, *ibid.*, **85**, 1337 (1963).

TABLE II

β ELIMINATION OF MERCAPTIDES FROM S-BENZHYDRYL- AND S-BENZOYL-L-CYSTEINE PEPTIDES DURING METHANOLYSIS

Peptide	Solvent[a]	Concn of peptide, *M*	β elimination,[b] %
VII	MeOH	0.013	0.24
VII	MeOH	0.0015	0.4
VIII	DMAc	0.026	23.4, 26.3
VIII	DMAc	0.022	21.5
VIII	MeOH–DMAc (1:3)	0.021	16.5
VIII	MeOH–DCAc (1:1)	0.021	10.0
VIII	MeOH–DMAc (3:1)	0.021	7.4, 7.8

[a] Solutions contain 1 equiv of 0.077 *N* sodium methoxide in methanol. [b] Percentage of β elimination is equated to the percentage of pyruvic acid found in the reaction mixture after 5 hr at 25°.



VIII

L-cysteinylglycylglycylglycyl-S-benzoyl-L-cysteinylglycinate[11] (VIII), was only slightly soluble in methanol and dissolved readily in only N,N-dimethylacetamide; therefore, the methanolysis of the S-benzoyl group was conducted with 1 equiv of sodium methoxide in N,N-dimethylacetamide. Under these conditions a substantial amount of β elimination occurred, as evidenced by the formation of *ca.* 20% of pyruvic acid upon acid hydrolysis of the reaction mixture. Although the site of β elimination (cysteine 1 or 5) was not established, the amount of β elimination occurring in VIII during removal of the S-benzoyl group was clearly related to the polarity of the solvent. When the methanolysis reaction was carried out in various mixtures of methanol and N,N-dimethylacetamide, the amount of pyruvic acid detected in the reaction mixture after hydrolysis decreased. From these data it appears that the utility of base-labile protective groups in peptides containing cysteine will depend on the base strength of the particular system employed for removal of the protective group. With larger peptides which require highly polar solvents for solution, β elimination of alkyl mercaptides from S-alkylcysteine residues may become an important and serious side reaction.

Experimental Section[12]

Ethyl N-carbobenzoxy-*S*-benzyl-L-cysteinylglycinate (IV),[5a] ethyl N-carbobenzoxy-*S*-benzhydryl-L-cysteinylglycine (V),[13] and ethyl N-carbobenzoxy-*S*-trityl-L-cysteinylglycinate[13] were prepared by the reported procedures.

Preparation of N-Carbobenzoxy-S-benzhydryl-L-cysteine N-Hydroxysuccimide Ester.—A solution containing 7.41 g (0.0176 mol) of N-carbobenzoxy-S-benzhydryl-L-cysteine[13] and 2.2 g (0.0176 mol) of N-hydroxysuccinimide in 12 ml of 1,2-dimethoxyethane was cooled to 0° and treated with 3.7 g (0.018 mol) of N,N-dicyclohexylcarbodiimide. The solution was stirred for 2 hr at 0° and 20 hr at 25°. The precipitated DCU was washed with 15 ml of 1,2-dimethoxyethane and the filtrate was evaporated *in vacuo*. The resulting solid was recrystallized from 250 ml of hot 2-propanol to provide 7.06 g (77.4%) of the ester, mp 131.5–132.5°.

Anal. Calcd for $C_{28}H_{26}N_2O_6S$: C, 64.85; H, 5.05; N, 5.40; S, 6.18. Found: C, 65.17; H, 5.23; N, 5.46; S, 6.45.

Preparation of N-Carbobenzoxy-S-benzhydryl-L-cysteinylglycine.—To a solution containing 2.59 g (0.005 mol) of N-carbobenzoxy-S-benzhydryl-L-cysteine N-hydroxysuccinimide ester in 15 ml of 1,2-dimethoxyethane was added a solution containing 0.38 g (0.005 mol) of glycine and 0.84 g (0.010 mol) of sodium bicarbonate in 13 ml of water. The solution was stirred for 5 hr at 25°, diluted with 75 ml of water, and acidified to pH 2 with 6 *N* hydrochloric acid. The solution was saturated with sodium chloride and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried, and evaporated *in vacuo* to a solid. Recrystallization from a 1:10 mixture of ethyl acetate–petroleum ether (bp 30–60°) provided 1.99 g (83%) of the peptide, mp 114–117.5°, $[\alpha]^{28}D$ −0.8° (*c* 0.5, $CHCl_3$).

Anal. Calcd for $C_{26}H_{26}N_2O_5S$: C, 65.25; H, 5.48; N, 5.85; S, 6.70. Found: C, 65.36; H, 5.53; N, 5.83; S, 6.92.

The same material, mp 111–116°, was obtained in 83% yield by hydrolysis of *t*-butyl N-carbobenzoxy-S-benzhydryl-L-cysteinylglycinate with boron trifluoride diethyl etherate in glacial acetic acid.

Ethyl Nα-Carbobenzoxy-Nε-*t*-butyloxycarbonyl-L-lysylglycinate.—A solution containing 2.79 g (0.02 mol) of ethyl glycinate hydrochloride and 11.23 g (0.02 mol) of Nα-carbobenzoxy-Nε-*t*-butyloxycarbonyl-L-lysine N,N-dicyclohexylammonium salt[14] in 20 ml of methylene chloride and 2 ml of chloroform was cooled to 0° and treated with 4.21 g (0.022 mol) of 1-ethyl-3-(N,N-dimethylaminopropyl)carbodiimide hydrochloride. The reaction mixture was stirred at 0° for 1.5 hr and at 25° for 11 hr. The solution was filtered and washed with 50 ml of ethyl acetate, and the filtrate was evaporated to an oil. The oil was dissolved in 150 ml of ethyl acetate and washed with 1 *N* sulfuric acid, water, 5% potassium bicarbonate, water, and saturated brine. The dried ethyl acetate solution was concentrated *in vacuo* to 100 ml, cooled, and filtered. The product, yield 8.1 g (87%), appeared as a white solid, mp 110.5–112°, homogeneous by tlc (system A).

Anal. Calcd for $C_{23}H_{35}N_3O_7$: C, 59.34; H, 7.58; N, 9.03. Found: C, 59.58; H, 7.60; N, 9.21.

Preparation of Ethyl N-Carbobenzoxy-S-benzhydryl-L-cysteinylglycyl-Nε-*t*-butyloxycarbonyl-L-lysylglycinate (Ia).—A solution of 11.62 g (0.025 mol) ethyl Nα-carbobenzoxy-Nε-*t*-butyloxycarbonyl-L-lysylglycinate in 250 ml of absolute ethanol containing 1.2 g of 10% palladium-on-charcoal catalyst was treated with a stream of hydrogen. After 0.5 hr, tlc (system C) indicated one spot and the suspension was filtered with the aid of diatomaceous earth. The filtrate was concentrated to 50 ml and treated with 250 ml of dry ether and 17.5 ml (0.245 mol) of 1.4 *M* hydrogen chloride in 2-propanol. The dried hydrochloride salt, yield 8.42 g (91.2%), mp 109–116°, was homogeneous by tlc (system C) and was used without further purification.

A solution containing 2.47 g (0.005 mol) of N-carbobenzoxy-S-benzhydryl-L-cysteinylglycine and 1.89 g (0.005 mol) of the crude hydrochloride in 11 ml of dry chloroform was cooled to −10° and treated with 0.69 ml (0.05 mol) of triethylamine. The resulting slurry was treated with 1.05 g (0.0055 mol) of 1-ethyl-3-(N,N-dimethylaminopropyl)carbodiimide hydrochloride and stirred at −10° for 1 hr and at 25° for 12 hr. The solution was evaporated *in vacuo* to provide a solid, which was dissolved in 300 ml of chloroform and washed with 100 ml of 1 *N* sulfuric acid and four 100-ml portions of water. The dried organic layer was concentrated to 50 ml and the peptide was precipitated by the addition of 700 ml of ether. Recrystallization of the resulting solid from dioxane–water gave 3.56 g (90%) of white solid, mp 162–164°, homogeneous by tlc (system A).

Anal. Calcd for $C_{41}H_{53}N_5O_9S$: C, 62.18; H, 6.75; N, 8.84; S, 4.05. Found: C, 62.33; H, 6.74; N, 9.03; S, 4.07.

Preparation of N-Carbobenzoxy-S-benzhydryl-L-cysteinylglycyl-Nε-*t*-butyloxycarbonyl-L-lysylglycine (Ib). Method A.—Attempts to saponify the ester Ia using alkaline conditions consistently resulted in the formation of a mixture of products, as shown by tlc (systems A and B). Saponification of 0.8 g (1.01 mmol) of Ia with 1 equiv of 0.95 *N* sodium hydroxide solution in dioxane at 25° was stopped after 3.5 hr by the addition of 1.5 equiv of cold 0.25 *N* hydrochloric acid solution. The solution was

(11) The synthesis of VIII will be reported in a separate paper.

(12) Melting points are uncorrected and were taken in unsealed capillary tubes or on a Kofler hot stage. Elemental analyses were performed by Microtech Laboratories, Skokie, Ill. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter. Mass spectral studies were conducted with a Hitachi Perkin-Elmer Model RMU-6E instrument.

The following solvent systems were employed for thin layer chromatograms: system A, chloroform–methanol (9:1); system B, chloroform–methanol–acetic acid (8.5:1:0.5); system C, chloroform (saturated with ammonia)–methanol (9:1); system D, benzene–ethyl acetate (8:2); system E, chloroform–methanol (19:1).

(13) L. Zervas and I. Photaki, *J. Amer. Chem. Soc.*, **84**, 3887 (1962).

(14) L. Zervas and C. Hamalidis, *ibid.*, **87**, 99 (1965).

extracted with ethyl acetate; evaporation of the organic extract yielded an oil which crystallized upon addition of methanol to provide 0.01 g (2.5%) of needles, mp 149–151° (lit.[15] mp 151–152°), homogeneous by tlc (R_f 0.95, systems A, B, and D). The mass spectrum (direct probe at 260°, 2.6 kV dynode, 0.5 slit width) exhibited peaks at m/e (rel intensity) 199 (6.3) attributed to $(C_6H_5)_2CHS^+$ and a pattern from 167 (100) down consistent with $(C_6H_5)_2CH^+$. These data are consistent with the structure of benzhydryl disulfide.

Method B.—A solution of 0.323 g (0.0011 mol) of N$^\epsilon$-*t*-butyloxycarbonyl-L-lysylglycine and 0.170 g (0.002 mol) of sodium bicarbonate in 3 ml of water was treated with a solution containing 0.576 g (0.001 mol) of N-carbobenzoxy-S-benzhydryl-L-cysteinylglycine N-hydroxysuccinimide ester in 5 ml of dimethoxyethane. The reaction mixture was stirred for 18 hr at room temperature, diluted with 100 ml of water, and acidified to pH 3 with 1 *N* sulfuric acid. The precipitate was filtered, washed with 50 ml of water, and dried *in vacuo* to yield 0.71 g of crude product. The substance was washed with ethyl acetate and ether and recrystallized from chloroform–hexane to provide 0.62 g (82%) of white solid, mp 134–139°, $[\alpha]^{28}D$ −22.6° (*c* 0.53, DMF).

Anal. Calcd for $C_{39}H_{49}N_5O_9S \cdot 0.5H_2O$: C, 60.60; H, 6.52; N, 9.06; S, 4.15. Found: C, 60.59; H, 6.45; N, 9.07; S, 4.08.

Preparation of *t*-Butyl N-*o*-Nitrophenylsulfenyl-S-benzoyl-L-cysteinylglycinate.—A solution of 5.60 g (0.01 mol) of N-*o*-nitrophenylsulfenyl-S-benzoyl-L-cysteine N,N-dicyclohexylamine salt[16] in 20 ml of chloroform at −10° was treated with 1.30 ml (0.01 mol) of isobutyl chloroformate and stirred at −10° for 10 min. The solution was then treated with 1.68 g (0.01 mol) of *t*-butyl glycinate hydrochloride and 1.01 g (0.01 mol) of N-methylmorpholine in 10 ml of chloroform. The reaction mixture was stirred for 2 hr at 0° and 5 hr at 25°. The solution was evaporated *in vacuo* and the residue was suspended in an ether ethyl acetate mixture. The suspension was filtered and the filtrate was washed with 0.5 *N* sulfuric acid, water, 10% potassium bicarbonate, water, and saturated brine. The dried extract was evaporated *in vacuo* to a yellow oil which was dissolved in chloroform, slurried with 5 g of silica gel, and filtered. The resulting solution was evaporated *in vacuo* to give 4.48 g (91%) of a yellow foam, homogeneous by tlc (system A). An analytical sample was prepared by crystallization from benzene–ether–hexane, mp 81–83°, $[\alpha]^{27}D$ −10.6° (*c* 1.37, $CHCl_3$).

Anal. Calcd for $C_{22}H_{25}N_3O_6S_2$: C, 53.75; H, 5.13; N, 8.55; S, 13.08. Found: C, 53.29; H, 5.15; N, 8.75; S, 13.29.

Preparation of *t*-Butyl N-Carbobenzoxy-S-benzhydryl-L-cysteinylglycyl-N$^\epsilon$-*t*-butyoxycarbonyl-L-lysylglycyl-S-benzoyl-L-cysteinylglycinate (VII).—To a solution of 4.48 g (0.091 mol) of *t*-butyl N-*o*-nitrophenylsulfenyl-S-benzoyl-L-cysteinylglycinate in 300 ml of dry ether was added 18 ml of 2.2 *N* hydrogen chloride in ether. An oil formed after 2 hr at 25°, the supernatant was decanted, and the oil was crystallized from chloroform–ether to give 2.09 g of *t*-butyl S-benzoyl-L-cysteinylglycinate hydrochloride, homogeneous (ninhydrin, iodine vapor) by tlc (system A).

A solution of 1.553 g (2.04 mmol) of IIb and 0.283 ml (2.04 mmol) of triethylamine in 15 ml of N,N-dimethylacetamide was treated with 0.25 ml (2.08 mmol) of pivaloyl chloride at −10°. After 10 min, 0.763 g (2.04 mmol) of crude *t*-butyl S-benzoyl-L-cysteinylglycinate hydrochloride and 0.283 ml (2.04 mmol) of triethylamine in 5 ml of N,N-dimethylacetamide was added to the reaction mixture. The solution was stirred at −10° for 1 hr and at 25° for 6.5 hr. The suspension was filtered and washed with ether and ethyl acetate, and the filtrate was added to 400 ml of ether. The supernatant was decanted and the gum was triturated with ether to give 1.91 g of solid. The material was filtered through silica gel G with 2% methanol in chloroform (v/v). The effluent was evaporated *in vacuo* and the solid was recrystallized from hot 95% ethanol–water (40:30, v/v) to give 1.616 g (73%) of VII: mp 174–180°; $[\alpha]^{26}D$ −23.0° (*c* 0.50, DMAc); homogeneous by tlc (system A, E).

Anal. Calcd for $C_{55}H_{69}N_7O_{12}S_2$: C, 60.92; H, 6.41; N, 9.04; S, 5.91. Found: C, 60.91; H, 6.29; N, 9.08; S, 5.98.

Preparation of *t*-Butyl N-Carbobenzoxy-S-benzhydryl-L-cysteinylglycyl-N$^\epsilon$-*t*-butyloxycarbonyl-L-lysylglycyl-L-cysteinylglycinate.—To a cooled solution of 324.5 mg (0.3 mmol) of VII in 300 ml of dry methanol was added 6 ml (0.33 mmol) of an 0.055 *N* solution of sodium methoxide in methanol. The reaction, followed on tlc with system E, required 2.5 hr for completion. The solution was acidified with 0.5 ml of glacial acetic acid, concentrated *in vacuo* to 50 ml, and poured into 700 ml of water. The washed precipitate was dried *in vacuo* to yield 283.8 mg (96.5%) of thiol: mp 185–188°; $[\alpha]^{28}D$ −10.8° (*c* 0.250, DMAc); homogeneous by tlc (system E).

Anal. Calcd for $C_{48}H_{65}N_7O_{11}S_2$: C, 58.82; H, 6.68; N, 10.00; S, 6.54. Found: C, 58.80; H, 6.63; N, 9.86; S, 6.57.

When the methanolysis of VII was carried out in more concentrated solution (0.02 *M* rather than 0.001 *M*), a spot corresponding to II appeared on the tlc of the reaction mixture.

Pyruvate Analyses. A. Saponification Reactions.—The substrate (*ca.* 0.02 mmol) was accurately weighed into a hydrolysis tube and dissolved in sufficient solvent (ethanol or N,N-dimethylformamide) to give the desired substrate concentration. The solution was treated with 1.1 equiv of 1.0 *N* sodium hydroxide solution, and the reaction mixture was left at room temperature for 5 hr. Solvent was then evaporated *in vacuo*, and 1 ml of constant-boiling 6 *N* hydrochloric acid solution was added. The tube was sealed and heated at 110° for 5 hr to liberate, by hydrolysis,[8] pyruvic acid from the dehydroalanine peptide present in the reaction mixture. The contents of the tube were carefully washed into a 5-ml volumetric flask with 1.1 *M* potassium hydrogen phosphate, the pH was brought to 7.5 with 50% sodium hydroxide, and the solution was diluted to volume with phosphate buffer. Aliquots of this solution were then analyzed for pyruvic acid with reduced diphosphopyridine nucleotide and lactic dehydrogenase as previously described.[8]

B. Methanolysis Reactions.—The substrate (*ca.* 0.01 mmol) was accurately weighed into a hydrolysis tube and dissolved in sufficient solvent (methanol, N,N-dimethylacetamide, or a mixture of both) to give the desired substrate concentration. One equivalent of 0.074 *N* sodium methoxide in methanol was then added, and the reaction mixture was allowed to stand at room temperature for 5 hr. The reaction mixture was then treated as described above. In all saponification and methanolysis reactions, the presence of unreacted starting material was observed by tlc (system A).

Registry No.—Ia, 22423-71-8; Ib, 22423-72-9; VII, 22423-77-4; N-carbobenzoxy-S-benzhydryl-L-cysteine N-hydroxysuccinimide ester, 22423-73-0; N-carbobenzoxy-S-benzhydryl-L-cysteinylglycine, 22423-74-1; ethyl N-carbobenzoxy-N$^\epsilon$-*t*-butyloxycarbonyl-L-lysylglycinate, 21869-27-2; *t*-butyl N-*o*-nitrophenylsulfenyl-S-benzoyl-L-cysteinylglycinate, 22423-76-3; *t*-butyl N-carbobenzoxy-S-benzhydryl-L-cysteinylglycyl-N$^\epsilon$-*t*-butyloxycarbonyl-L-lysylglycyl-L-cysteinylglycinate, 22423-78-5.

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(16) L. Zervas, D. Borovas, and E. Gazis, *J. Amer. Chem. Soc.*, **85**, 3660 (1963).

Synthesis of Lamprolobine

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The two-step reaction sequence of partial hydrogenation of 1-alkyl-3-acylpyridinium salts and acid-catalyzed cyclization of the resultant 1-alkyl-3-acyl-2-piperideines has formed the basis of general synthesis of quinolizidines[2] and alkaloids based on this ring system.[3] Heretofore only methyl nicotinate, nicotin-

(1) Public Health Service Predoctoral Fellow, 1966–1969.

(2) E. Wenkert, K. G. Dave, and R. V. Stevens, *J. Amer. Chem. Soc.*, **90**, 6177 (1968), and references cited therein.

(3) E. Wenkert, *Accounts Chem. Res.*, **1**, 78 (1968).